Rejection of Claims 2-6, 8-12, and 19-21 Under 35 U.S.C. § 112, First Paragraph

Although the Examiner agrees with Applicant that the specification is enabling for the treatment of macrophage related disorders, the Examiner maintains the rejection of claims 2-6, 8-12, and 19-21 under 35 U.S.C. §112, first paragraph, as not enabling the *prevention* of such disorders. The Examiner bases this rejection on "the large number of diseases encompassed by the recited claims which may have multiple causes or origins."

Applicant respectfully traverses the rejection. The Examiner asserts that the presently claimed methods are not enabled for prevention due to the "the large number of diseases encompassed by the recited claims which may have multiple causes or origins." However, Applicant respectively points out that the claims encompass only ***those diseases characterized by aberrant activity or number of macrophages within a selected tissue area of a subject.*** This does not cover an undue number of diseases, but rather a subset of diseases which have a ***common cause or origin***, namely aberrant activity and/or numbers of macrophages within a localized tissue area. It is this common cause that is addressed by way of the presently claimed invention. Moreover, claim 21 is limited to a particular subset of such diseases. Therefore, the claims are commensurate in scope with the support provided in the disclosure.

As previously noted, the disclosure provides ample data from *in vivo* studies evidencing enablement of both prevention and treatment of diseases caused by aberrant activity and/or numbers of macrophages within a localized tissue area. For instance, Example 9 provides studies and data from relevant animal models having chronic skin diseases characterized by aberrant macrophage activity and/or numbers - and demonstrates that the claimed method ***both treats and prevents*** the symptoms of the disease, even for a prolonged period of time. Applicant further provides specific techniques for determining the presence of aberrant macrophage activity or numbers within a selected tissue area by, for example, taking a tissue biopsy and assaying it for the presence of macrophage PO activity or macrophage numbers using, e.g., macrophage specific antibody staining (e.g., see page 45, lines 5-14). Accordingly, the animal model

used applies to other diseases claimed that are of similar etiology because there is a nexus between the data provided for chronic skin disease and other diseases caused by aberrant macrophage activity and/or numbers, and the skilled artisan would recognize that Applicant's results are appropriately extrapolated to such diseases.

Thus, the *in vivo* data provided in Applicant's disclosure constitutes unequivocal evidence that diseases characterized by aberrant activity or numbers of macrophages can be treated and/or prevented using the claimed method and, thus, that Applicant's disclosure meets the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, it is respectfully requested that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-6 Under 35 U.S.C. § 102 (a)

The Examiner maintains the rejection of claims 1-6 under 35 U.S.C. §102 (a) as being anticipated by Curnow, R. (*Cancer Immunol. Immunother.* 45:210-215 (1997)) as evidenced by Graziano *et al.* (*J. Immunol.* 155:4996-5002 (1995)). In particular, the Examiner alleges that Curnow teaches that "down modulating CD64 by CD64 specific antibodies reduces the activity of CD64 bearing cells such as macrophages" and that the agent disclosed by Graziano has the function of the claimed invention.

Applicant respectfully traverses this rejection. As amended, claims 1-6 are drawn to a method of selectively reducing the number or activity of ***macrophages within a selected area of tissue*** using a combination of an agent which specifically binds to an Fc receptor present on macrophages *via* an Fc receptor and an agent which kills or reduces the activity of the macrophages.

By contrast, Curnow teaches that mAbH22 (i.e., MDX-33) binds to ***circulating monocytes*** and causes down modulation of CD64 (FcγRI) thereby providing a potential treatment for ***monocyte-mediated*** disorders, such as ITP. Curnow fails to teach or suggest treatment of non-circulatory and/or macrophages-mediated disorders characterized by ***an aberrant number or activity of macrophages within a selected tissue*** (e.g., the skin) of a subject. Indeed, the mAbH22 taught by Curnow is only administered to the circulatory system where monocytes exist, not to selected areas of tissue where macrophage reside.

Moreover, Curnow (page 213, col. 2, second full paragraph) merely states that "evidence suggest[s] that...e.g., monocytes and macrophages express Fc receptors" and notes that "CD64 specific antibodies [have] been shown to down-modulate CD64 significantly." This statement in no way teaches or suggests the use of a composition comprising an agent which binds to an Fc receptor on macrophages and further comprises an agent which kills or reduces the activity of macrophages to treat macrophage-mediated disorders characterized by an aberrant "number or activity of macrophages", as claimed by Applicant. Therefore, Curnow fails to anticipate the presently claimed invention.

Graziano *et al.* is cited merely as evidence that H22, as taught by Curnow, binds the FcγRI receptor outside the natural ligand binding site and can be used to treat human diseases. However, this reference, like Curnow, also fails to teach or suggest the specific use of H22 to reduce ***"the number or activity of macrophages within a selected area"*** (e.g., as recited in claim 1) much less, as a method to treat or prevent ***macrophage-mediated disorders within a selected area of a subject*** (e.g., as recited in claims 2-6).

As neither reference recites each and every element of the claims as amended, it is respectfully requested that the rejection under 35 U.S.C. § 102 (a) be reconsidered and withdrawn.

Rejection of Claims 1-6 and 18 Under 35 U.S.C. § 102 (b)

The Examiner also maintains the rejection of claims 1-6 and 18 under 35 U.S.C. §102 (b) as being anticipated by Ericson *et al.* (*British Journal of Haematology*, 92:718-724 (1996)). The Examiner states that Ericson *et al.* teaches a monoclonal antibody that can bind and down modulate FcγRI receptor on circulating monocytes, e.g., in ITP patients, and thus, which has the function of the agents recited in the present claims.

Applicant respectfully traverses this rejection. As pointed out above, the claims as amended are drawn to a particular method of using a composition made up of an agent which binds to an Fc receptor on macrophages and further comprises an agent that can reduce the number or activity of ***macrophages within a selected area of tissue*** of a subject by contacting the composition with the tissue area. Ericson *et al.* fail to teach or test this particular use for their mAb, let alone the use of a composition as claimed which

contains both an agent that can bind a macrophage and an agent that can reduce the number or activity of a macrophage.

Moreover, like Curnow, Ericson *et al.* only teach administration of their mAb to peripheral blood mononuclear cells, that is, circulating monocytes -- ***not macrophages within a selected area of a tissue***, as claimed by Applicant.

Accordingly, it is respectfully requested that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejection of Claims 1-2, 8-12, and 21 Under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-2, 8-12, and 21 under 35 U.S.C. §103(a) as being unpatentable over Curnow, R.T. (cited *supra*), Graziano *et al.* (cited *supra*), Ericson *et al.* (cited *supra*), Uhr *et al.* (USPN 5,686,072), Ghetie *et al.* (USPN 5,578,706), Rybak *et al.* (USPN 5,840,840), Pastan (USPN 5,489,525), and Bjerke *et al.* (ACTA Derm. Venereol. (Stockh) Suppl. 186:141-142 (1994)).

In particular, the Examiner states that, contrary to Applicant's assertion, Curnow and Ericson *et al.* do teach the treatment of macrophage-mediated disorders as claimed by Applicant. In particular, the Examiner asserts that Curnow teaches that "monocytes and macrophages that express Fc receptors...play an important role in platelet destruction" and that since "CD64 specific antibodies down modulate CD64 significantly" these antibodies "may be useful in treating the autoimmune disease of ITP." The Examiner also argues that Ericson *et al.* teach the down modulation of FcγR1 on macrophages which are known to be major effectors in platelet destruction. The Examiner therefore concludes that, in combination with the remaining eight (8) references relating to immunotoxins, it would have been obvious to one of ordinary skill in the art at the time of the invention to have arrived at the claimed invention.

Applicant respectfully traverses this rejection. Applicant was the first to recognize that certain diseases, such as skin diseases and other autoimmune diseases, are primarily caused by ***aberrant activity and/or numbers of macrophages within a localized area of tissue***, (not by freely circulating monocytes as taught in the prior art) and was the first to develop a method for selectively eliminating or reducing the activity

of such macrophages to effectively treat such diseases using e.g., a macrophage-specific immunotoxin. As described, in the present specification and examples, this required extensive characterization of macrophages as they reside within a selected tissue area (e.g., area of skin), to establish relevant in vivo models that demonstrate the role of aberrant macrophage number or activity in disease, and validate methods for treating or preventing such macrophage-mediated disease within a selected tissue area, e.g., in a subject.

None of the cited references, either alone or in combination, teach or suggest the treatment of such ***macrophage-mediated disorders*** which exist within a ***localized area of tissue*** as opposed to in the circulatory system, let alone in the manner taught by Applicants. As previously pointed out, Curnow, Graziano, and Ericson each teach methods of targeting ***circulating monocytes – not macrophages*** which reside within selected tissue areas, as claimed by Applicant. Moreover, the mere teaching by Curnow and Ericson that monocytes and macrophages have common Fc receptors that can be down-modulated by agents that bind to the receptors and that macrophages are involved in platelet destruction would ***not*** have made it obvious to use such agents in combination with agents which kill macrophages to treat macrophage-mediated disorders in localized tissues. In fact, ***neither Curnow nor Ericson even examine or study macrophages on any level.***

In this regard, it is also relevant to note that monocytes and macrophages are two distinct cell types that occupy two distinct compartments of the body, respectively, the peripheral blood and tissue, such as, e.g., skin, lung, and liver (see Cellular and Molecular Immunology, Abbas *et al.*, 4th Ed., 2000, and also the specification at, e.g., page 37, lines 12-20). Accordingly, studies on circulating monocytes in the peripheral blood do not correlate with studies on macrophages within a selected area of tissue. Stated another way, a method of treating monocytes in the peripheral blood is not an indication as to how a different cell type, a macrophage, is going to respond in a tissue. For example, there is no reasonable expectation that introducing an agent intravenously (as taught by Curnow and Ericson *et al.*), would even contact a macrophage in a tissue. Accordingly, intravenous methods for treating circulating monocytes in the peripheral

blood would not suggest that such a method, with any reasonable expectation of success, could be applied to macrophages within a selected area, e.g., a tissue.

For at least these reasons, Curnow, Ericson *et al.*, and Graziano either alone, or in combination, fail to teach or suggest the claimed invention, as amended.

As Applicant has previously asserted, the references of Uhr, Ghetie, Rybak and Pastan fail to make up for this deficiency, since they pertain only to immunotoxins and ***teach nothing about the treatment of macrophage-mediated diseases***.

In particular, Uhr teaches therapies for targeting B cells (not macrophages) via an epitope unrelated to an Fc receptor. B cells are derived from a lymphoid precursor which is a completely different hematopoietic lineage from macrophages which are derived from a myeloid precursor. Ghetie is a mere general review discussing how to make antibody/immunotoxins and also fails to teach or suggest the use of the antibody/immunotoxins specifically to treat macrophage-mediated diseases. Similarly, Rybak discloses antibody/immunotoxins (in particular, an RNAse toxin) and fails to teach or suggest the use of such antibody/immunotoxins specifically to treat macrophage-mediated diseases. Pastan also fails to teach or suggest the use of the antibody/immunotoxins to treat macrophage-mediated diseases, as the authors teach only the treatment of prostate cancer cells.

Like the above-discussed references, Bjerke also fails to teach or suggest any method of selectively preventing or treating macrophage-mediated diseases. This reference merely teaches the use Fc binding antibodies to monitor changes in Fc receptor levels in response to therapy – not as a therapy and certainly not to reduce macrophage activity or numbers as claimed by Applicant.

Thus, overall, based on the fact that none of the cited references speak to the prevention or treatment specifically of ***macrophage-mediated disorders within a localized area*** of tissue, as claimed by Applicant, it would not have been obvious to have combined the individual teachings of these references in any manner, let alone in the manner claimed by Applicant, to have arrived at the claimed invention. The present rejection is clearly based on hindsight and <u>not</u> on what was taught by the prior art at the time of the invention. Recently, the Federal Circuit noted that "[a] critical step in

analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Werner Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313 (Fed. Cir. 2000).

Accordingly, based at least on the foregoing, it is respectfully requested that the rejection under 35 U.S.C. § 103 (a) be reconsidered and withdrawn.

Rejection of Claims 1 and 13-17 Under 35 U.S.C. §103 (a)

The Examiner maintains the rejection of claims 1 and 13-17 under 35 U.S.C. §103(a) as being unpatentable over Curnow, R.T. (cited supra), Graziano *et al.* (cited supra), Ericson *et al.* (cited supra), in view of McGrath *et al.* (USPN 5,580,715), Estis *et al.* (USPN 5,026,557), Rodwell *et al.* (USPN 4,671,958), Lifson *et al.* (USPN 4,869,903), and Bagshawe (USPN 5,658,568). In particular, the Examiner states that, in combination, the newly cited references of McGrath, Estis, Rodwell, Lifson, and Bagshawe disclose the targeting of macrophages with a immunotoxin and a liposome using, for example, an antibody or antibody fragment that binds to FcγRI as taught by Curnow, Graziano, and Ericson *et al.* Thus, based on the combination of these eight (8) references, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to have arrived at the claimed invention.

Applicant respectfully traverses this rejection. As previously pointed out above, Curnow, Graziano and Ericson *et al.* fail to teach or suggest any method of selectively reducing the number or activity of macrophages within a selected area using an Fc receptor binding agent, as claimed by Applicant.

McGrath fails to make up for this deficiency. While the reference refers to the targeting of macrophages using a liposome-based agent, this is carried out using anti-CD-14 and not an agent that binds to an Fc receptor, as claimed by Applicant. In fact, McGrath teaches away from the present invention given that the main cellular expression of CD14 is on monocytes and not macrophages (see, e.g., pg. 398 of *Cellular and Molecular Immunology* by Abbas *et al.*, W.B. Saunders Co. 1991).

Estis merely teaches the preparation of adjuvants comprising liposomes, and thus fails to make up for the previously discussed deficiencies. Moreover, adjuvants are recognized as substances for increasing an immune response and thus would not have been thought applicable to the goal of selectively reducing numbers or activity of macrophages to treat particular macrophage-mediated diseases.

Rodwell teaches antibody independent uptake of liposomes in macrophages, and thus also teaches away from any Fc binding agent-mediated method of selectively killing macrophages, such as that claimed by Applicant. While the reference states that liposomes are readily phagocytosed by macrophages, it also teaches that this is dependent on "[w]hether or not the liposomes are coated with antibody molecules" (Col. 2, lines 35-38). Accordingly, the reference would not have been considered relevant to the goal of Fc receptor mediated macrophage-specific cellular killing.

Lifson teaches the targeting of a protein using a carrier anti-macrophage antibody, but solely to prevent HIV replication or infection and not to reduce the activity or number of macrophages as claimed by Applicant. Moreover, the reference neither teaches nor suggests targeting a macrophage using an Fc receptor binding agent.

Bagshawe also fails to render the claimed invention obvious in any way since it does not teach or suggest targeting of macrophages whatsoever, much less using an Fc binding agent of the claimed invention.

Overall, the Examiner has simply combined both here and in the foregoing §103(a) rejection, using hindsight, references which at best teach a general component used in the novel and inventive method of the invention. The Examiner has ***not*** provided evidence of the requisite motivation for why, at the time of the invention (i.e., ***without*** the benefit of hindsight) one of ordinary skill would have been motivated to have combined these references in the manner suggested by the Examiner). Indeed, the mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

Overall, based on the above, the cited combination of references fails would not have rendered obvious at the time of the present invention a method of selectively

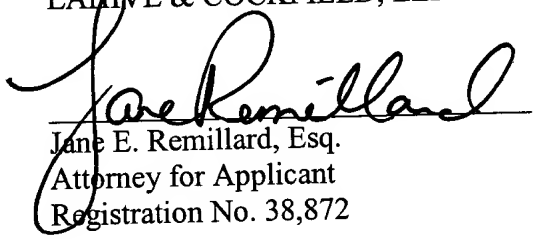
reducing the number or activity of ***macrophages within a selected area*** (e.g., to treat a disorder characterized by aberrant numbers or activity of macrophages) using an agent which ***specifically binds to macrophages via an Fc receptor*** and an agent which kills or reduces the activity of the macrophages, as claimed by Applicant. Again, the rejection is clearly based on hindsight and ***not*** on what was taught by the prior art at the time of the invention. *In re Werner Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313 (Fed. Cir. 2000).

Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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Attachment: Appendix A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of [selectively] reducing the number or activity of macrophages within a selected area of tissue of a subject, comprising contacting the tissue area with a macrophage-binding compound comprising (a) an agent which binds to an Fc receptor on macrophages at a site which is distinct from that bound by the natural ligand binding site for the receptor [endogenous immunoglobulins to]; and (b) an agent which kills or reduces the activity of the macrophages.

Appendix A

1. A method of reducing the number or activity of macrophages within a selected area of tissue of a subject, comprising contacting the tissue area with a macrophage-binding compound comprising (a) an agent which binds to an Fc receptor on macrophages at a site which is distinct from that bound by the natural ligand binding site for the receptor; and (b) an agent which kills or reduces the activity of macrophages.

2. A method of treating or preventing a disease in a subject characterized by aberrant activity or number of macrophages within a selected area of the subject, comprising locally administering to the area a macrophage-binding compound comprising (a) an agent which binds to an Fc receptor; and (b) an agent which kills or reduces the activity of the macrophages.

3. The method of either of claims 1 or 2, wherein the agent which binds to an Fc receptor binds at a site which is not bound by an endogenous immunoglobulin.

4. The method of either of claims 1 or 2, wherein the Fc receptor is an Fcγ receptor (FcγR) or an Fcα receptor (FcαR).

5. The method of claim 4, wherein the Fcγ receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII.

6. The method of claim 5, wherein the Fcγ receptor is a human FcγRI.

8. The method of either of claims 1 or 2, wherein the macrophage-binding compound comprises an anti-Fc receptor antibody conjugated to a toxin.

9. The method of claim 8, wherein the anti-Fc receptor antibody is an anti-Fc γ receptor antibody or a fragment thereof.

10. The method of claim 9, wherein the anti-Fcγ receptor antibody is a monoclonal antibody selected from the group consisting of mab 22, 32 and 197, or a fragment thereof.

11. The method of claim 9, wherein the anti-Fcγ receptor antibody is a humanized antibody H22 produced by the cell line having ATCC accession number CRL 1117 or a fragment thereof.

12. The method of claim 8, wherein the toxin is selected from the group consisting of Gelonin, Saporin, Exotoxin A, Onconase and Ricin A.

13. The method of claim 1, wherein the agent which kills or reduces the activity of the macrophages is encapsulated within a liposome.

14. The method of claim 13, wherein the agent which kills or reduces the activity of a macrophage is dichoromethylene diphosphonate (CL2MDP) or derivatives thereof.

15. The method of claim 13, wherein the agent which binds to an Fc receptor is a single chain antibody.

16. The method of claim 13, wherein the agent which binds to an Fc receptor is an anti-Fcγ receptor antibody or a fragment thereof.

17. The method of claim 13, wherein the agent which binds to an Fc receptor is a single chain anti-Fcγ receptor antibody or a fragment thereof.

18. The method of claim 1, wherein the contacting step occurs in culture.

19. The method of either of claims 1 or 2, wherein the macrophage-binding compound is administered topically, intradermally or subcutaneously in a pharmaceutically acceptable carrier.

20. The method of claim 2, wherein the disease is characterized by enhanced proliferation and/or growth factor secretion of the macrophage.

21. The method of claim 2, wherein the disease is selected from the group consisting of psoriasis, atopic dermatitis, scleroderma, cutaneous lupus erythematosis, Human Immunodeficiency Virus infection, multiple sclerosis, rheumatoid arthritis, Chronic Polymorphic Light Dermatosis, Chronic Obstructive Pulmonary Diseases, and Wegener's Granulomatosis.